REMARKS

I. Status of the Claims

Claims 1-21 were originally filed. As the result of a restriction requirement, claims 15-21 have been withdrawn from consideration. Upon entry of the present amendment, claims 3 and 5 as well as all withdrawn claims are canceled. Claims 1, 2, 4, and 6-13 are amended to add the word "isolated," which finds support throughout the specification, particularly in the examples. Claims 1 and 14 are amended to move "(SEQ ID NO:9)" to directly behind the sequence "$X^1X^2SLX^3V$" and to replace "an" before "amino acid" with "any" in order to avoid possible confusion. This amendment is supported by the description of SEQ ID NO:9 provided in the sequence listing. Claims 1 and 14 are also amended to delete the phrase "or is absent" following the word "methionine." This amendment finds support in the exemplary polypeptides, *e.g.*, SEQ ID NOs:10 and 11. Claim 8 is further amended to recite the full name "eosinophil derived neurotoxin" when the abbreviation "EDN" is first used in the claims, which is supported by the specification, *e.g.*, on page 9, line 13. No new matter is introduced by the amendment. Applicants note with appreciation that the Examiner has indicated the allowability of claim 4, except for its dependency from a rejected claim.

II. Claim Objection

Claim 8 was objected to for using an abbreviation ("EDN") that is not defined the first time it is used. The present amendment has addressed the objection.

III. Claim Rejections

A. 35 U.S.C. §101

Claims 1, 3, 5, and 9-13 were rejected under 35 U.S.C. §101 for allegedly covering non-statutory subject matter, *i.e.*, naturally occurring, non-manmade material. As amended, claims 1-13 now recite the word "isolated." Applicants submit that this rejection is obviated in light of the present amendment.

B. 35 U.S.C. §112, Second Paragraph

Claims 1, 3, 5, and 8-14 were rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Specifically, the Examiner stated that the language in claim 1: "X^3 represents an amino acid residue (SEQ ID NO:9)" is unclear as to its precise meaning. As amended, claims 1 and 14 now recite "$X^1X^2SLX^3V$ (SEQ ID NO:9), wherein X^1 represents methionine, X^2 represents glycine or is absent, and X^3 represents any amino acid residue." This language makes it clear that SEQ ID NO:9 refers to the sequence $X^1X^2SLX^3V$. Applicants thus submit that the indefiniteness rejection is overcome.

C. 35 U.S.C. §112, First Paragraph

Claims 1, 3, 5-7, and 9-14 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse the rejection, particularly in light of the present amendment.

A claimed invention is enabled when the disclosure allows one of ordinary skill in the art to make and use the invention without undue experimentation. MPEP §2164.01. The test for enablement, as set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), requires the consideration of multiple factors: the breadth of the claims; the nature of the invention; the state of the prior art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Upon entry of the present amendment, claims 3 and 5, which recite 90% homology, are canceled. The remaining claims are directed to an isolated RNase A superfamily polypeptide having a defined N-terminus sequence (SEQ ID NO:9) and selective toxicity to a proliferating endothelial cell. Thus, the claimed polypeptide has well defined structural and functional features and the claim scope is not overly broad.

In raising the enablement rejection, the Examiner apparently took the position that the pending claims broadly cover any RNase polypeptide or any RNase polypeptide having 90% identity to SEQ ID NO:2 or 4. Applicants cannot agree. The claimed polypeptide belongs to the

"RNase A superfamily," a term that is precisely defined in the specification from page 8, line 25, to page 9, line 12:

> "The RNase A superfamily," refers to a group of ribonucleases that are homologous to bovine pancreatic ribonuclease A in sequence, and are enzymes which are transferases or phosphodiesterases that can catalyze the hydrolysis of ribonucleic acid. They exist in many different organisms such as mouse, hamster, pig, ox, human, deer, hippopotumas, etc. The RNase A superfamily polypeptides share a common characteristics in that they are homologous to bovine pancreatic RNase A.

In the same paragraph, the specification further identifies a number of known members of the RNase A superfamily, such as frog lectin from Rana *catesbaiana*, onconase, eosinophil derived neurotoxin (EDN), human eosinophil cationic protein (ECP), angioginin (ANG), and bovine pancreatic RNase, and the references describing these proteins. Also in the same paragraph, the specification refers to Figure 1 of the application and points out the that amino acid sequence alignment among the known RNases as presented in Figure 1 illustrates not only the existence of highly conserved domains but also the precise location and identity of the conserved amino acid residues. Based on this description and Figure 1, Applicants contend that one of skill in the art would be able to readily identify a member of the RNase A superfamily, for example, based on sequence alignment such as the one shown in Figure 1; the artisan would also be able to readily create a functional variant of a known family member through sequence modification, for example, based on the sequence comparison results shown in Figure 1, which identify the crucial and non-crucial amino acid residues for preservation of functionality.

Another factor to be considered is the N-terminal sequence of the claimed polypeptide. Because the N-terminal sequence has only limited flexibility, Applicants contend that the claim scope does not encompass every RNase polypeptide. Moreover, the required cytotoxicity of the claimed RNase polypeptide further defines the claim scope in a functional aspect.

Given the level of knowledge and technical skill in the art, Applicants believe that these claims are fully enabled, because one of skill in the art would know after reading the

instant specification: first, what constitutes an "RNase A superfamily" polypeptide and how to make it, *e.g.*, by sequence comparison such as shown in Figure 1 and by a recombinant method; second, whether a particular polypeptide sequence has an N-terminus that fits within SEQ ID NO:9 and how to modify a polypeptide such that its N-terminus fits the profile; and third, how to test a given RNase polypeptide for its selective toxicity to a proliferating endothelial cell.

The specification contains ample directions to practice the claimed invention, such as how to modify an RNase A superfamily polypeptide (*see, e.g.*, page 11, line 1, to page 17, line 3, and the examples) and how to test the selective toxicity to the proliferating endothelial cells (*see, e.g.*, page 19, line 10, to page 21, line 19). The level of technical sophistication is high in the art, and the claimed RNase superfamily polypeptides can be readily tested according to the methods commonly used by those skilled in the art or the methods taught by the specification (such as the functional assays for cytotoxicity toward proliferating endothelial cells) to eliminate inoperable embodiments. MPEP §2164.01 states, complex experimentation is not necessarily undue, if the art typically engages in such experimentation. In the present case, although some experimentation may be involved to practice the claimed invention using embodiments other than those explicitly described in the application (*e.g.*, a polypeptide having the amino acid sequence of SEQ ID NO:2 or 4), such experimentation utilizes well-established techniques and is the type routinely conducted in the art. Thus, any necessary experimentation would not constitute undue experimentation.

Accordingly, Applicants respectfully request the withdrawal of the enablement rejection.

D. 35 U.S.C. §102

Claims 1, 3, 5, and 8-11 were rejected under 35 U.S.C. §102(b) for alleged anticipation by Sakakibara *et al.* (1992) as evidenced by Griffith *et al.* (1997). Applicants respectfully traverse the rejection in light of the present amendment.

To anticipate a pending claim, a prior art reference must provide, either expressly or implicitly, each and every limitation of the pending claim. MPEP §2131. As amended, the

pending claims are directed to an isolated RNase A superfamily polypeptide having a defined N-terminal sequence and having a selective toxicity to proliferating endothelial cells. The N-terminal sequence is characterized as $X^1X^2SLX^3V$ (SEQ ID NO:9), where X^1 is methionine, X^2 is glycine or is absent, and X^3 is any amino acid.

In contrast, the Sakakibara reference describes an RNase isolated from urine of pregnant women, RNase UpI-2, which apparently has the N-terminal sequence of SLHV (see Figure 3 on page 327 of the Sakakibara reference). This reference therefore does not provide an RNase that has an N-terminal sequence fitting the profile of SEQ ID NO:9. Neither has the Examiner identified anything in the reference that suggests the modification of the N-terminus of an RNase in this manner.

As such, Applicants contend that, because all limitations of the pending claims are not found in the Sakakibara reference, the claims are not anticipated. The withdrawal of the anticipation rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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